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Investigating the role of ACE2 Receptors in the rate of COVID-19 infectivity in smokers and Opioid abusers: A Review

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Abstract

It seems necessary to understand the association of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), with its entering bronchoalveolar and brain cells, which have a high concentration of angiotensin-converting enzyme 2 (ACE2). Although the virus infects healthy people, the rate of infection and mortality is higher and significant in vulnerable people, such as drug users and addicts who have acute and chronic respiratory disease. It also places a heavy economic burden on families and societies around the world. Thus, researchers are aiming to provide prevention and treatment strategies to people at risk. The purpose of the present study was to collect studies on the rate of infection with coronavirus in people who abuse drugs. Besides, the role of the ACE2 receptor as a key factor in coronavirus infectivity in these people was investigated. Our narrative review on the relationship between COVID-19 and opioid abuse and smoking, with consideration of ACE2's role, contains original and human studies. According to the results of the current study, those who smoke or are dependent on opioids are much more likely to experience COVID-19-related respiratory side effects or even pass away.

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Highlights

What is current knowledge?

- Coronavirus enters susceptible cells through ACE2 receptors.
- Opioid abuse and smoking increase ACE2 expression.
- The possibility of coronavirus entrance in smokers and opioid abusers increases through the ACE2 receptors.
- Getting infected with COVID-19 in opioid abusers and smokers causes an excessive increase in the immune system and induces a cytokine storm and irreversible effects compared to other people who are infected with the coronavirus.

What is new here?

- Trying to reject the hypothesis that smokers and opioid abusers do not suffer from the corona virus.

Introduction

Since December 2019, when the World Health Organization (WHO) reported that coronavirus had spread in Wuhan, China, and then around the world, more than 200 million people have been infected and more than 4 million people have died (1). Numerous studies have been published on the function of the coronavirus and how it affects the cells and organs, especially in the respiratory system (2). This virus, like its ancestral family, severe acute respiratory syndrome coronavirus (SARS-CoV), binds to the surface of the respiratory epithelial cells and brain neurons through the interaction of its surface spike glycoprotein with ACE2 enzymic receptor on host cells. After entering the cells, the virus imposes irreversible effects by overstimulating the immune system and triggering high levels of systemic inflammation, called a "cytokine storm" (3, 4). The destructive effects of this virus on the respiratory system of people with underlying respiratory diseases such as chronic obstructive pulmonary disease (COPD) caused by smoking (5) and opioid abuse (6, 7) have caused more concern.

Previous studies have also shown that smokers and opioid-dependent persons are more likely to have influenza, MERS-COV, and infectious diseases (8). According to Arcavi et al., cigarette smokers and passive smokers were more susceptible to pneumonia (with prevalence rates of 51% and 17%, respectively) (9). Chen et al. examined the opioid agonists and human influenza A/WSN/33 (H1N1) virus. They showed that methadone therapy significantly augmented H1N1 viral replication in human lung epithelial A549 cells (10). The highest rate of complications caused by coronavirus was related to people with a history of smoking (about 27.3% among the community of 78 patients with COVID-19) (11). The results of published clinical studies in 2020 and 2021 indicate that smokers and addicts are at higher risk of coronavirus than healthy individuals (12).

The above evidence reinforces the hypothesis that smoking and opioid addiction are associated with the development of severe acute respiratory syndrome coronavirus 2. In other words, these studies have shown that substance addiction increases the expression of ACE2 receptors and their upregulation (13, 14), thereby weakening the immune system (15, 16). In contrast, a few studies suggest that the consumption of some of these substances reduces inflammation caused by the coronavirus by regulating the immune system (17, 18).

Therefore, while the world is in a state of emergency and needs to provide possible and new solutions to prevent, treat, and reduce the effects of this emerging phenomenon, it is essential to study the possible interference mechanisms of smoking and abuse of addictive substances, such as opioids, on respiratory cells infection with coronavirus. Therefore, the hypothesis that addicts are vulnerable to COVID-19 should be examined.

Results and Discussion

Cigarette smoking and opioid abuse terminology

Cigarette, as the largest preventable risk factor for morbidity and mortality in developed countries, is made of dried broad-leaved tobacco plants from the *Nicotiana* genus and the *Solanaceae* (nightshade) family that originally grew in North and South America and is now cultivated worldwide (19). Smokers are at risk for lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases (CVD) due to exposure to a variety of toxic and carcinogenic substances in cigarettes (20). Besides, with the development of respiratory lung disease, the true and vital capacity of the lungs is greatly reduced, and the risk of fatal diseases increases (21). Cigarettes contain more than 4,500 carcinogenic and mutagenic toxins (22) that induce irreversible effects on the respiratory system and the immune system. One of the toxins in cigarettes is nicotine alkaloid, which is a psychoactive and addictive chemical. Due to its molecular similarity to acetylcholine (Ach), this substance is released in synaptic spaces and replaces acetylcholine. With continued smoking, after a while, chemical receptors do not respond to acetylcholine, and therefore, the transmission of neural messages is repeated and done through nicotine; then, with increasing smoking, dependence and addiction are created. Causing harm to the respiratory system and compromising the immune system can increase the likelihood of being more vulnerable to COVID-19. The results of studies by many researchers in various centers, including the World Health Organization, indicate that smoking, hookah, and tobacco weaken the respiratory system of heavy smokers. Therefore, the hypothesis that smoking is associated with acute respiratory syndrome caused by coronavirus is reinforced. New research also shows that smoking increases the expression of the ACE2 receptor (13), resulting in better and more virus-binding to the cell and more severe coronavirus infection by weakening the immune system (15).

An opiate is a term classically used in pharmacology to mean natural or semisynthetic alkaloid derivatives found in the resin of the opium poppy plant, *Papaver somniferum*. An opioid is a more modern term and refers to a drug (natural and synthetic) that interacts with the opioid receptor in the brain (23).

Around 12% of opium is made of the analgesic alkaloid morphine, which is processed chemically to produce heroin and other semisynthetic (hydromorphone, hydrocodone, oxycodone, oxymorphone, ethylmorphine, buprenorphine, and fentanyl) or fully synthetic opioids (fentanyl, pethidine,

levorphanol, methadone, tramadol, tapentadol, and dextropropoxyphene) and antagonist drugs such as naloxone. These synthetic opioids are made for medicinal use and for the illegal drug trade (23). There are endogenous opioid peptides produced naturally in the body, like endorphins, enkephalins, dynorphins, and endomorphins. Morphine is produced in small amounts in the body (24).

Opioids are absorbed from the gastrointestinal tract, nasal mucosa, and lung subcutaneous. Three types of opioid receptors have been definitively known: mu (μ), kappa (κ), and delta (δ), which are linked to opioid abuse and addiction (25). Central nervous system (CNS) regions like the thalamus, hypothalamus, pituitary, amygdala, hippocampus, olfactory areas, cortex, and spinal cord (26) are the primary sites of action of opioids, which affect the function of organs by changing the secretion of brain neurotransmitters and neuropeptides. All three receptors have analgesic properties. The μ and δ are immune-modulator and exist on various cells of the immune system, and κ and μ types are respiratory depressors and affect respiratory rhythm-regulating neurons (23). It is important to note that opioid receptors also exist in the bronchial epithelium, nerve fibers, and glands of bronchial walls (27).

According to the United Nations Office on Drugs and Crime (UNODC) estimation, there are 16 million opioid users in the world (18). Although therapeutic uses of opioids are prescribed to reduce the pain, cough, and shortness of breath caused by COVID-19 (28), long-term use and opioid addiction or opioid abuse have irreversible effects on the immune system that predispose people to coronavirus infection. According to findings, it seems that the rate of catastrophic conditions in opium-addicted patients who are infected with the coronavirus is higher than that of normal people with COVID-19 (29, 30). Studies have shown that the weakening of the immune system in people with opioid addiction is such that even the rate of coronavirus infection is fatal for some of them (31). The rate of mortality in opioid-abusing hospitalized patients with COVID-19 during the pandemic was 9.6% (32).

The effect of cigarette smoking and opioid abuse on the coronavirus cell entry

According to other studies (2,14), Brake et al. confirmed that cytological brushings and microarray analysis of human airway epithelia and type-2 pneumocytes showed that the gene expression level and activity of the ACE2 protein in smokers and opioid abusers are significantly higher than in healthy people (33). This finding was completely consistent with animal studies (34). Although some studies suggest that increased levels of ACE2 expression are associated with reduced lung damage in the mouse model (35), the situation is quite different with coronavirus infection. Coronavirus, like other viruses in the corona family (SARS-CoV), binds to the ACE2 receptor, which acts as an entering receptor for the virus and inhibits its function. Indeed, based on Kuba and Rivellese et al., coronavirus reverses the beneficial effects of ACE2 on the protection of lung damage by inhibiting the enzyme converting angiotensin II into angiotensin 1-7 or ACE2 (36, 37). Therefore, if the expression of ACE2 proteins increases for any reason on the surface of respiratory epithelial cells or respiratory regulatory cells, the probability of these receptors being occupied by the coronavirus also increases, which, in turn, increases the virus entry. Therefore, the possibility of inducing virus infection also increases. Since cigarette smoke and opioid substances increase ACE2 expression, people addicted to these are more prone to pneumonia or respiratory failure caused by the coronavirus (38).

On the contrary, the results of some studies reported less damage induction to the respiratory system caused by smokers and opioid abusers compared to normal people. According to these studies, nicotine in cigarette smoking, morphine, and dynorphin bind to ACE2 receptors (14), destroy the respiratory cell, and prevent the virus from entering the cells; thus, the virus itself is also destroyed. It has also been suggested that nicotine glue can reduce the contamination of COVID-19 and reduce the number of people seeking medical attention (39). Of course, these findings do not seem to be credible because they contradict the basic function of ACE2 receptors, how they interact with the virus, and how the virus enters the cell. On the other hand, nicotine and nicotine glue are toxic substances, and with the consumption of each cigarette, a significant amount of nicotine enters the body in milligrams. If we assume that nicotine can prevent the virus from entering the body, it makes the body more prone to infection, and in the cell bed, it triggers an unrestrained stimulation of the immune system (16).

Stimulation of the immune system by inducing a more severe cytokine storm can worsen the general condition of the patient with the virus. Results of Schultze et al. in 2021 showed that smokers are most affected by COVID-19, respiratory infections, and lung disease because the virus occupies more cellular receptors and enters the cell more easily (40). In addition, according to pathophysiological data, an increased risk of infections for individuals with substance use disorders (SUD) is also more likely (16).

Lukassen's study reported that ACE2 proteins, in addition to being predominantly present in alveolar type 2 (AT2) cells (41), can also be expressed on the surface of ciliated cells like goblet cells in the airways and on secretory cells of bronchial branches epithelial of the lung, which are underappreciated in the SARS-CoV-2 infection studies (42). Osan et al. evaluated the expression of ACE2 in the COVID-19 inflammatory model on the respiratory tract epithelium of patients with chronic obstructive pulmonary disease (COPD) caused by smoking. They found that goblet cell proliferation and hyperplasia, along with increased ACE2 expression, were more common in people infected with the coronavirus who already had COPD due to smoking than in the healthy group (43). Therefore, it is likely that targeting and replication of viruses through goblet cells with high levels of ACE2 is also increased and permissive to SARS-CoV-2 infection. Thus, goblet cells may be a new target of coronavirus infection in the respiratory epithelium.

Studies have discovered that other cells in the respiratory system, such as club cells, can also express ACE2, but this increase in expression is not enough to be effective for the entrance of the virus. Therefore, it can be concluded that the effective increase of ACE2 is associated with coronavirus infection.

Besides the ACE2, other cofactors are needed for the virus to enter, without which the virus cannot enter the epithelial cells. Transmembrane protease serine 2 (TMPRSS2), which is expressed in epithelial cells of the lungs, prostate, and many other tissues, is an essential host co-factor for coronavirus entry into target cells (44). Voinsky et al. showed that the level of TMPRSS2 cofactor mRNA in bronchial epithelial cells was significantly higher in smokers than in non-smokers. Therefore, this condition may put them at a greater risk of infection with SARS-Cov-2 or coronavirus. (45). Hao et al. concluded that, interestingly, club cells that express the ACE2 are inefficient due to the lack of expression of this co-helper protein, TMPRSS2, in the entry of viruses into the mucosa of the respiratory system (46). If the TMPRSS2 is not expressed or inhibited by pharmacological drugs, the entry of the virus into the cell is reduced. Therefore, TMPRSS2 could be an attractive target and offer new potential to be seriously considered for SARS-CoV-2 antiviral therapy.

The spike protein of coronavirus contains a Furin cleavage site that is mainly responsible for the host membrane fusion of the virus. This site does not exist in other coronavirus types. Therefore, this unique feature of the coronavirus allows it to enter the target cells by attaching to the host membrane and leading to infection (47). It should be noted that in smokers, the amount of Furin protein also increases, which is associated with increased viral infectivity in the respiratory system of these people. (48).

The search for an infectious link between COVID-19 by increasing the entry of opioid-influenced goblet cells, club cells, and cofactors has yielded no results; still, opioids increase the expression of the ACE2 receptors in the respiratory airway and CNS neurons and induce a cytokine storm. Induction of a cytokine storm and oxidative stress as a result of opioid abuse along with COVID-19 damage the connections between the brain microvascular endothelial cells (BMVEC) of the blood-brain barrier and increase the permeability of this barrier to pathogens and toxins that induce irreversible brain complications and neuro-inflammation and can lead respiratory depression and pneumonia (12, 49). Long-term use of opioids such as cocaine and morphine increase SIRT1 (sirtuin 1) and SIRT2 expression, which binds to the promoter region of the ACE2 gene and increases the expression of ACE2 (50, 51).

From the above, it can be concluded that people with substance use disorder (SUD) and smokers have a higher possibility of having the virus enter their respiratory epithelium due to the increased expression of the ACE2 protein. Moreover, smokers with increasing cofactors' expression, which is necessary for the entry of viruses such as TMPRSS2 and Furin, are more likely to get an acute respiratory infection caused by the virus.

The effects of cigarette smoking on coronavirus cell infection

Nicotinic acetylcholine receptors (7α nAChRs) are present on the surface of type 2 alveolar epithelial cells, pulmonary macrophages, bronchial epithelium, and pulmonary endothelial cells (52-54), which normally lead to tissue protection by preventing the production of inflammatory cytokines (55).

According to Farsalinos and Sifat et al.'s studies, in a person with a history of smoking and developing COVID-19, the interaction of the coronavirus with nicotine in cigarette smoke upsets the anti-inflammatory balance of nicotine in the body and by inversely affecting its acetylcholine receptors, it increases the activity of the angiotensin-producing type 2 axis or ACE2 /ATII/AT1 (54), stimulates pulmonary macrophages (54, 56); based on Farsalinos' results, it consequently increases the expression of the nuclear factor kappa B (NFκB). NFκB plays an important role in the increase of the transcription of inflammatory cytokines, such as interleukins 1 beta and 6 (IL-1β and 6) and tumor necrosis factor-alpha (TNF-α), which induces oxidative stress and damages the respiratory epithelium (55).

Nicotine in cigarettes also reduces the activity of the angiotensin 1-7 production pathway or ACE2/AT (1-7)/mass receptor in people with coronavirus disease. After the coronavirus enters the respiratory cells via the ACE2 receptor, both the virus itself and the nicotine in cigarette smoke inactivate the angiotensin 1-7 production pathway. Inactivation of this pathway leads to activation of the ACE/ATII/AT1 pathway, increases the production of inflammatory cytokines, and induces oxidative stress (57), thereby leading to severe inflammation (56, 58).

Nicotine acetylcholine receptors (7α nAChRs) also increase the expression of ACE2 in smokers (57, 59), which in turn increases the entry of the coronavirus into epithelial cells and their proliferation. It causes the formation of new viruses and the production and secretion of virus-associated proteins from the infected cell, which, in turn, induces new molecular events (4). After the detection of

viruses by macrophages in adjacent alveolar sacs, sequential mechanisms are activated as a cascade of pathophysiological mechanisms. These mechanisms eventually lead to the overproduction of a number of inflammatory substances such as cytokines and many pro-inflammatory chemokines, including IL-2, IL-7, and TNF-α, and macrophage inflammatory protein 1α (MIPIα) and MIPI1β, which are involved in invoking other immune cells to cause more severe inflammation caused by a cytokine storm (13). Therefore, since smoking increases the severity of the inflammatory response associated with COVID-19, smokers respond more strongly to the infection caused by COVID-19 (60) (Figure 1).

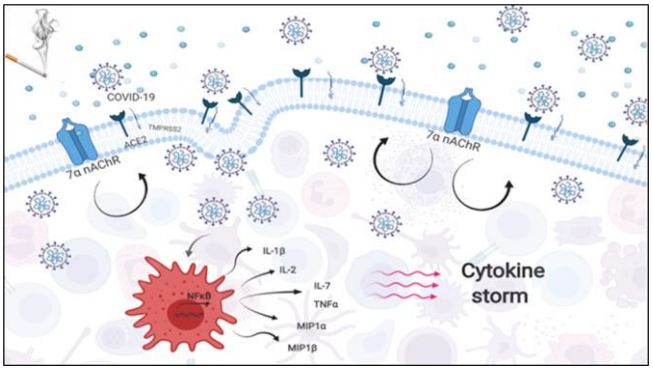

Figure 1 Effects of nicotine in cigarettes on exacerbation of COVID-19 infection in alveolar epithelial cells. Nicotine acts on its receptor (7α nAChRs) and activates the expression of ACE2 and coronavirus entry. Then, the coronavirus activates the macrophage for the production of inflammatory cytokines and induces an unbridled cytokine storm. 7α nAChRs: Nicotine acetylcholine receptors, ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane serine protease 2, IL: Interleukin, MIP: Macrophage inflammatory protein.

According to the literature, blood levels of nitric oxide (NO) are elevated both by smoking and by stimulation of nicotinic acetylcholine receptors stimulated by nicotine in cigarette smoke (61). Nitric oxide at physiological concentrations acts as an anti-inflammatory agent and immunosuppressant and is a toxic substance for invading and infectious microorganisms (62). If a person smokes and is exposed to the coronavirus, NO reduces the presence of the coronavirus in the respiratory system by stimulating an increase in the motility of the respiratory cilia, stimulating mucus secretion, inducing antimicrobial effects, dilating the bronchi, and increasing oxygen delivery (63).

Martel et al. decelerated that in repeated smoking, NO levels tend to pathophysiological concentrations; in addition to inhibiting the antiviral activity of the respiratory epithelium, it leads to an increased presence and entry of coronavirus into the upper and lower parts of the respiratory system (63) and can also act as a pro-inflammatory agent and intensify inflammatory responses. In the immune system and inflammatory processes, the main focus is on the inducible nitric oxide synthase (iNOS) as a possible isoform involved in the immune and inflammatory responses. Overproduction of NO by the enzyme iNOS, when inflamed, is inherently toxic because overproduction of nitric oxide by this enzyme inactivates the respiratory chain enzymes in mitochondria and induces cell death (64) (Figure 2).

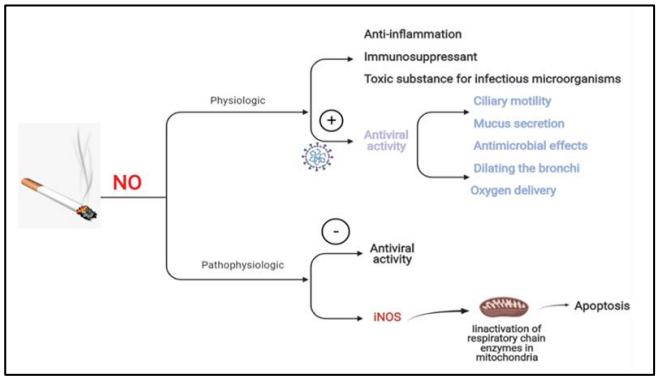

Figure 2 Effects of cigarette smoking on nitric oxide levels in physiological and pathological conditions. Blood levels of nitric oxide (NO) are elevated both by smoking and by stimulation of nicotinic acetylcholine receptors stimulated by nicotine in cigarette smoke. If a smoker person is exposed to the coronavirus, NO reduces the presence of the coronavirus in the respiratory system by stimulating an increase in the motility of the respiratory cilia, stimulating mucus secretion, inducing antimicrobial effects, dilating the bronchi, and increasing oxygen delivery. When, due to repeated smoking, NO levels tend to be at pathophysiological concentrations, in addition to inhibiting the antiviral activity of the respiratory epithelium, they induce inducible nitric oxide synthase, which is involved in the immune and inflammatory responses. Finally, this cytokine cascades lung cell apoptosis was cause d. iNOS: Inducible nitric oxide synthase.

From the above, it can be concluded that nicotine in cigarettes is due to increased ACE2 protein expression, as well as increased virus entry, increased ACE/ATII/AT1 inflammatory axis activity, and decreased ACE2/ AT (1-7)/ mass receptor, an anti-inflammatory axis activity. This creates a higher chance of exacerbating the occurrence of cytokine storms caused by coronavirus in the respiratory epithelium. Therefore, no other role can be considered in reducing the incidence of COVID-19 patients in smokers.

Furthermore, the presence of toxic compounds such as lead in cigarette smoke also increases the response of components involved in stimulating the immune system, such as lymphocytes T helper 2, which increases the secretion of other inflammatory cytokines such as interferon-gamma (IF-γ), interleukins 1 and 12 (IL-1,12), and tumor necrosis factor-alpha (TNF-α), causing inflammation and stimulating the immune system (65). Therefore, the synergistic effect of Pb inflammation with the inflammatory effect of coronavirus due to increased virus entry through ACE2 receptors induced by nicotine in cigarettes leads to a more severe cytokine storm and severe immune system stimulation and, finally, will have irreparable complications to the lungs (Figure 3).

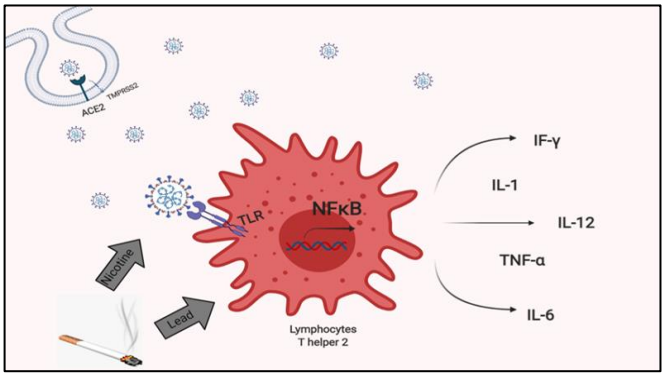

Figure 3 Effects of cigarette smoking ingredients on exacerbation of COVID-19 infection. Lead in cigarette smoke increases the response of components involved in stimulating the immune system, such as lymphocytes T helper 2, which increases the secretion of other inflammatory cytokines and stimulates the immune system. Therefore, the synergistic effect of Pb inflammation with the inflammatory effect of coronavirus due to increased virus entry through ACE2 receptors induced by nicotine in cigarettes leads to a more severe cytokine storm and severe immune system stimulation and will, finally, cause irreparable complications to the lungs. ACE2: Angiotensin-converting enzyme 2, TMPRSS2: Transmembrane serine protease 2, TLR: Toll-like receptor 2, IL: Interleukin, TNF-α: Tumor necrosis factor α, IF-γ: Interferon-gamma, NFκB: Nuclear factor kappa B.

Additional research indicates that among individuals who smoke over extended periods, alveolar epithelial cells release inflammatory mediators like cytokines, chemokines (66), and enzymes such as caspase 3, 7, and 9. This process can result in chronic inflammation, apoptosis of epithelial cells, lung damage, and contribute to the development of smoking-related health issues (67, 68). The coronavirus also enters the lung parenchyma cells and destroys them after proliferation, further stimulating the immune system and thus exacerbating both cell destruction and inflammation due to lung parenchyma cell destruction, which will have destructive effects (3). Therefore, in smokers, cigarette smoke, such as firewood, ignites inflammation and destruction of parenchymal cells (Figure 4).

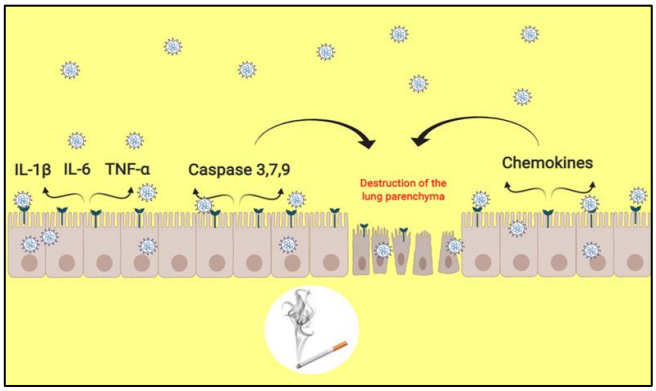

Figure 4 Effects of cigarette smoking on respiratory epithelial cells infected with the coronavirus. In long-term smokers, alveolar epithelial cells secrete inflammatory mediators such as cytokines and chemokines, along with a variety of proteases such as caspase 3, 7, and 9, which induce chronic inflammation, leading to apoptosis of epithelial cells and the progressive destruction of the lung parenchyma, and induce pathogenesis of smoking and further inflammation. By entering, multiplying, and destroying the lung parenchyma, the coronavirus intensifies the effect of smoking, and these effects are intensified in the destruction of the lung parenchyma. IL: Interleukin, TNF-α: Tumor necrosis factor α.

The effects of opioid abuse on coronavirus cell infection

According to numerous reports, drug abuse is a prevalent chronic psychiatric

disorder worldwide, which causes powerful physical and psychological desires for brain-altering substances. It is linked to infectious diseases transmitted through sharing contaminated injection or inhalation tools (69). However, studies on the mechanism of the effect of opioid abuse (heroin, fentanyl, morphine) on the infectivity of COVID-19 are very limited, while opioid abuse is likely to increase the development of acute lung injury and exacerbation of COVID-19 infection.

In general, opioid substances like endogenous opioid system (β-endorphins, dynorphins, and enkephalins), through the tight link to three classes of opioid receptors, μ (MOR), δ (DOR), and k (KOR) in the brain stem (70), suppress the respiratory system and lead to slow and incomplete breathing in dependents, which leads to hypoxia; therefore, it should be monitored closely for worsening respiratory functions (71). There are complex interactions between opioid abuse and the involvement of other body systems, including the nervous, endocrine, renal, and cardiovascular systems (71, 72). Opioid use disorders have shown renal toxicity, acute kidney injury, accumulation of metabolites (72), reduced function of the liver (73), inhibited cardiac excitation-contraction process, decreased heart rate, and blood pressure (74), causing poor prognosis for those with COVID-19 infections and an increased risk of severe infections (75). For example, opiate users may misinterpret COVID-19 symptoms as opioid withdrawal and try to treat themselves by self-administering opioids, which has irreparable consequences (76). In addition, people addicted to opioids are afraid to go to medical centers because they refuse to have a urine test and tend to be treated remotely, which, in turn, leads to a desire for self-medication and a loss of time to recover from COVID-19 (16).

According to clinical investigations of Lin et al., COVID-19 infection may progress to severe forms in opioid addict patients, which is likely attributable to weakened immunity as a result of chronic consumption of substance drugs (14). One reason for the strengthening of COVID-19 infectivity can be attributed to the analgesic effects of opioids and the tendency to use them chronically during the treatment stages of COVID-19, which gradually weakens the immune system (77). Conversely, Lambert et al.'s findings validated that prolonged opioid abuse raises ACE2 function expression. Given that the ACE2 receptor is crucial for coronavirus entry, heightened receptor expression due to opioids elevates the likelihood of virus cell entry, potentially contributing to virus infection onset (31).

It should be noted that in people who use opioids for a long time, the immune system is weakened, which provides the basis for the infection of viruses that have entered the body cells through ACE2 expression and may lead to respiratory infections such as pneumonia (78) which increase the risk of death (79-81). Extremely inadequate ventilation and the sensation of suffocation of patients with chronic opioid use who are infected with the coronavirus and hospitalized in the intensive care unit (ICU) are evidence of the adverse effects of these substances (82, 83).

Some opioid abuse through the alternation of the hypothalamic-pituitary-adrenal (HPA) axis activity, which is responsible for systematic inflammation control, leads to the high secretion of the corticotrophin-releasing hormone (CRH), arginine-vasopressin (AVP), and adrenocorticotropic hormone (ACTH). Excessive ACTH secretion, with an effect on the adrenal gland, increases the secretion of glucocorticoids in the zona fasciculata of the adrenal cortex. Glucocorticoids, as an anti-inflammatory effector, inhibit the innate immune system pathway that occurs in the face of an infectious agent like coronavirus by reducing leukocyte recruitment, with detrimental effects on macrophages, neutrophils, dendritic cells, natural killer cells, mast cells, and B and T cell lymphocytes (84) which are involved in creating an antibody, pro-inflammatory cytokine-producing (TNF-α, IL-1β, 6, and18), cytotoxicity, and T cell-mediated immune responses. Thus, the increased level of glucocorticoids by opioid abuse results in higher affection of pathogen infections, slowing down the recovery process and causing severe disease progression in SARS-CoV-2 (70).

Although morphine reduces TNF-α levels and thereby suppresses the primary innate immune response (85), by desensitizing the HPA axis, it also results in inhibiting glucocorticoid release and increases the IL-1β which acts as pro-inflammatory cytokine and has significant actions in the emergence of various immune-mediated disorders (86). Morphine suppresses the immune system by apoptotic induction of immune cells, reduction of phagocytic activity, thymus, and spleen atrophy, and decrease of the proliferation of lymphocytes (87). Morphine, on the other hand, reduces the potency of phagocytic cells involved in pathogen removal through induced nitric oxide induction signaling (88). Studies have shown that morphine reduces the levels of antiviral cytokines, such as alpha and gamma interferons (IFN-α and IFN-γ); thus, virus replication increases (89). Therefore, people who abuse morphine are more likely to develop cytokine storms induced by SARS-CoV-2 infections and be exposed to serious and deadly complications (90).

Interestingly, chronic opioid use is associated with apoptosis and dysfunction of pulmonary endothelial cells through the induction of nitric oxide and the subsequent induction of oxidative stress (91) and increases endothelial cell permeability, which causes pulmonary edema and raises the risk of death in these individuals. Having COVID-19 will also make the situation worse (70, 92) (Figure 5).

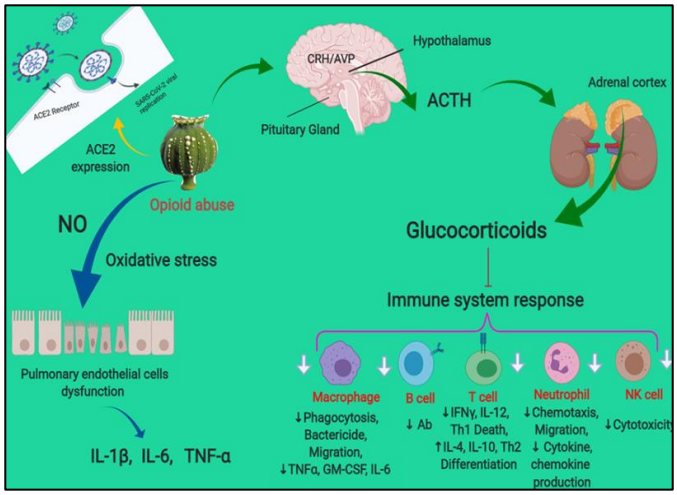

Figure 5 Effects of opioid abuse on exacerbation of COVID-19 infection. Opioid abuse increases the entry of the coronavirus by increasing the expression of ACE2 receptors and activating the immune system. By inducing oxidative stress, it causes disruption in the function of the lung parenchyma and increases the overstimulation of the immune system by increasing the level of inflammatory cytokines. Besides, by activating the hypothalamus-pituitary axis and increasing the production of ACH, it leads to the stimulation of the adrenal cortex, and by increasing the level of glucocorticoids, it leads to the seal of the immune system in the body's defense against the coronavirus. ACE2: Angiotensin-converting enzyme 2, CRH: Corticotrophin-releasing hormone, AVP: Arginine-vasopressin, ACTH: Adrenocorticotropic hormone, NK cell: Natural killer cell, IL: Interleukin, TNF-α: Tumor necrosis factor α, IF-γ: Interferon-gamma, Th: T helper, AB: Antibody, NO: Nitric oxide.

Summary

Although nicotine, opium, and cannabinoids may be potential therapeutics for infection of COVID-19 (anti-cough, covering the ACE2 receptor, or reducing its number on lung epithelial cells), their abuse will certainly disrupt the body's immune homeostasis (93). The review and compilation of numerous studies in the present study showed that people who smoke or are addicted to opioids have a much higher chance of developing respiratory adverse effects or even death from COVID-19 (12,16,38,45,78). Abuse of these substances increases the expression of the specific receptor (ACE2) for the entry of coronavirus on the surface of the respiratory or cerebral cells (94,95). For smokers and opioid users with compromised immune systems due to drug abuse, the likelihood of the virus entering the body and heightening immune system responses is elevated. This can result in a more severe cytokine storm (96). Finally, most respiratory epithelial cells are destroyed, which eventually exacerbates the infection and worsens the condition by destroying the body's homeostasis-stabilizing mechanisms. Therefore, substance abuse may increase mortality in people with COVID-19 (67,68). Therefore, when the world is exposed to the epidemic of this mysterious emerging global virus, mechanisms of action, warning, and awareness should be provided, such as the need to quit smoking and opioids; moreover, there is a need for health incentives, economic, and financial support to communities by governments or non-governmental organizations, appropriate scientific and health strategies to successfully quit smoking and opioid abuse in people involved, to reduce the risk of COVID-19 and increase survival.

Conclusion

According to the current study, the belief that smoking and opioid abuse reduce the risk of contracting COVID-19 during the pandemic is rejected with scientific investigations and putting together the physiological mechanisms like a puzzle.

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Ethical statement

No dataset was associated with the manuscript.
This article does not contain any studies on human participants or animals performed by any of the authors.

Conflicts of interest

There is no conflict of interest in the present study.

Author contributions

Narges Marefati: Design the study, Searching, Data curation, Writing-original draft, Rewising.

Hassan Ghoshooni: Writing-review & editing.

Mostafa Mahabadi: Supervision, Submitting.

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